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Meiotic Origin of Aneuploidy
An Overview

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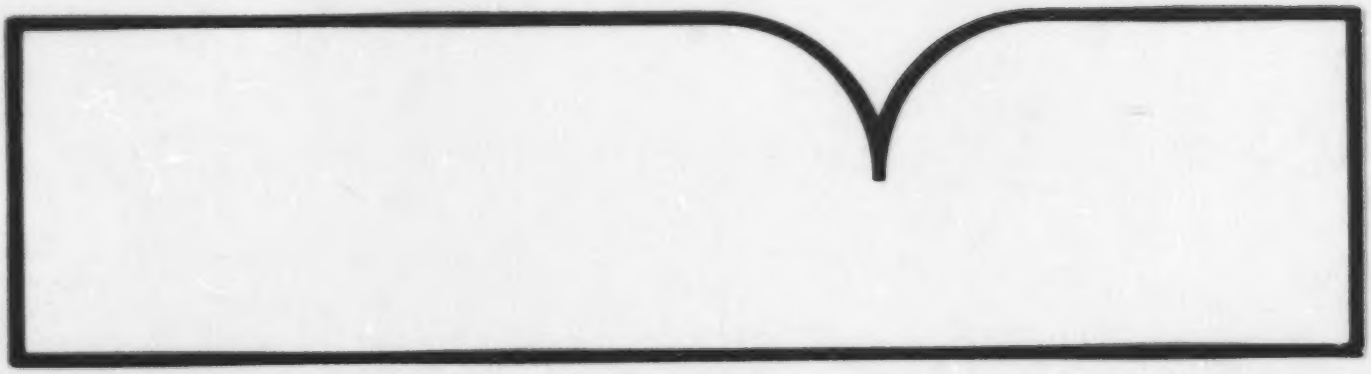

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by

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Aside from its adaptive potential, germ cell aneuploidy is usually considered a "mistake" with dire clinical consequences. The prevalence of aneuploidy in spontaneous abortions and various disabling syndromes of liveborn testifies to the importance of abnormal chromosome numbers arising at meiosis. While some fraction of these conditions may be attributable to embryonic chromosomal errors, it is believed that meiotic nondisjunction represents the primary mechanism. Apparently, meiotic trisomies arise from nondisjunction at metaphase I more often than at metaphase II. This is not surprising in view of the unique chromosomal activities occurring in the primary meiocytes which may be vulnerable to alterations predisposing these cells to aneuploidy. At this stage, errors in bivalent formation, crossing over, or segregation may lead to aneuploidy. Secondary meiocyte division is similar to mitosis and presumably is susceptible to the same types of anomalous segregation that can lead to aneuploidy in somatic cells. The intent of this overview is to summarize and integrate some of the current major concepts of meiotic aneuploidy development.

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MEIOTIC ORIGIN OF ANEUPLOIDY: AN OVERVIEW

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INTRODUCTION

Mammalian germ-line aneuploidy can occur as a highly evolved natural process. For the creeping vole, Microtus oregoni, and sex-reversed mice, it is actually a necessary step for completing gametogenesis (1). In the male germ cells of these rodent species, the presence of an X chromosome (in the vole) or an extra X chromosome (in sex-reversed mice) inhibits spermatogenic maturation. As a mechanism for eliminating the inhibitory X chromosome, mitotic chromosome nondisjunction occurs in the primordial germ cells of fetal testes of Microtus and the adult testis of sex-reversed mice.

Aside from its adaptive potential, germ cell aneuploidy is usually considered a "mistake" with dire clinical consequences. The prevalence of aneuploidy in spontaneous abortions and various disabling syndromes of liveborn testifies to the importance of abnormal chromosome numbers arising at meiosis (2). While some fraction of these conditions may be attributable to embryonic chromosomal errors, it is believed that meiotic nondisjunction represents the primary mechanism. Apparently, meiotic trisomies arise from nondisjunction at metaphase I more often than at metaphase II (3, 4). This is not surprising in view of the unique chromosomal activities occurring in the primary meiocytes which may be vulnerable to alterations predisposing these cells to aneuploidy. At this stage, errors in bivalent formation, crossing over, or segregation may lead to aneuploidy. Secondary meiocyte division is similar to mitosis (5) and presumably is susceptible to the same types of anomalous segregation that can lead to aneuploidy in somatic cells.

Increasing recognition of the health consequences of meiotic aneuploidy has stimulated much interest in etiological factors. It is generally believed that environmental influences and endogenous factors related to aging and

physiological predispositions are responsible. However, no major advances in clarification of the pertinent molecular or higher order events have been achieved. This can be attributed to the complexities of chromosome biochemistry and behavior during meiosis and the limitations of experimental approaches for reliably measuring aneuploidy. Incidences of this chromosomal condition in natural populations remain somewhat uncertain, and very little has been learned about environmental agents which may induce gametic aneuploidy.

Nevertheless, a number of cogent explanations of meiotic aneuploidy have been proposed. Taken together, they suggest a general progression of primary causes, mediating factors, and target cellular structures and functions (Fig. 1). This outline is not inclusive of all possible aneuploidy pathways which have been considered. For example, it does not directly address chromosome replicative "misfire" to give an extra chromosome copy. Bond and Chandley (6) have reviewed the existing evidence for this and concluded that, while possible, it probably is not a significant mechanism. The behavioral and functional chromosomal properties which theoretically provide mechanisms of germ cell aneuploidy generation are stage-specific (Table I). As indicated, chromosomal anomalies expressing at meiosis may have originated in the meiocyte or may have progressed there after arising in gonial cell types.

The mechanisms suggested in Table I are based on a variety of cellular functions and chromosomal properties, including mitotic events which should theoretically apply to meiosis as well as those which are exclusively meiotic. Several excellent aneuploidy reviews (4, 6, 7) which comprehensively cover meiosis have been invaluable resources for this more selective examination. The intent here is to summarize and put into perspective some of the current major concepts of meiotic aneuploidy development.

DRIVING FORCES

Although meiotic aneuploidy is the result of a complex series of metabolic events, there are basically three driving forces presumed responsible for its production: genetic background, physiological changes related to aging, and environmental induction.

It is not yet clear to what extent environmental induction may be operating as a causal factor in aneuploidy generation. However, one might expect that environmental factors could act either indirectly on general cellular physiology or directly on meiotic chromosomes and spindle structures to alter chromosome distribution at cell division. Induced aneuploidy in mammalian germ cells has been the subject of several recent reviews (4, 6, 8, 9, 10, 11) and will not be considered further here.

The occurrence of multiple cases of aneuploidy within a family group and evidence of elevated risk for trisomy recurrence after a first episode in young women hints that genetic controls may be operating (12). Mutant alleles affecting chromosome segregation are known to exist in Drosophila (13), and a locus required during meiotic segregation events as been described in yeast (14). However, direct evidence for similar genetic dictates in humans is lacking. Nevertheless, that there may be such constitutional bases for varying tendencies among individuals to develop aneuploid gametes seems likely. It has been suggested that grandparental consanguinity may result in parental homozygosity for genes causing nondisjunction (15). Some individuals may be cryptic mosaics with trisomic gonadal cells, or certain chromosome polymorphisims and rearrangements may effect aneuploid meiocytes (12).

Effects upon chromosome kinetics may be mediated by other genetically governed traits. For example, Warburton (12), in reviewing the unexplained

occurrence of high antithyroid antibody levels in parents of Down Syndrome offspring, has noted that these antibodies may be implicated in the origins of gametic aneuploidy. In summary, considerable data exist to suggest the importance of various genetic factors for aneuploidy tendencies. Unfortunately, these data are in no case very substantive, and firm conclusions cannot yet be drawn.

Few "trends" in aneuploidy occurrence are evident. However, the increasing incidence of aneuploidy with maternal aging is a classical association. There is conflicting evidence as to whether or not paternal aging may also be implicated (3, 16). The maternal age correlation does not apply to all chromosome monosomies and trisomies; however, it clearly characterizes Down Syndrome. A considerable body of literature has accumulated since the theory of a "production line" mechanism of oogenesis was proposed by Henderson and Edwards (17) to explain the association. They observed reduced chiasmata, increased univalents, and increased aneuploidy incidence in older mice and suggested that there may be gradients in the fetal ovary during development that could lead to differences in chiasma frequency along a "production line." Oocytes formed early in life would have higher chiasma frequencies and would be ovulated early in life. Later-formed oocytes, presumably more susceptible to chromosome segregation errors as a result of fewer chiasmata and more univalents, would be ovulated later. As indicated below, the validity of the "production line" hypothesis is in question.

In a recent account of spontaneous abortions and liveborn (18), it was estimated that the oocytes of older women are more often aneuploid than not. Age-related physiological changes in general may contribute to a gradual decline in the efficiency of chromosome activities, structure, or functions. In older individuals, loss or inactivation of centromeres (19) or failure in

the neuroendocrine control of meiosis (4) may be conducive to meiotic aneuploidy development.

Whatever the specific degenerative changes might entail, studies with uniovariectomized mice (20) have suggested that abnormal segregation of chromosomes in meiosis is a result of physiological as opposed to chronological aging. The long-term effects of uniovariectomy include fewer subsequent estrus cycles and an earlier onset of acyclicity--events associated with advanced maternal age. Chandley (20) suggests that any factor acting to deplete oocytes could advance the maternal age effect and enhance aneuploidy incidence.

METABOLIC MEDIATION

These major driving forces may act on diverse targets including chromosome structure, movement, and activites such as replication and recombination (Fig. 1). It is reasonable to assume that many of these actions are mediated by metabolism. Hormonal regulation of germ cell differentiation and maturation may interact with specific endogenous or exogenous changes to result in aneuploidy. For example, Hansmann and Jenderny (21) have studied oocytes from parental strains and F_1 crosses of NMRI/Han, C57/Bl, and Balb/c mice and from Djungarian hamsters after gonadotropin stimulation. F_1 hybrid females from the NMRI/Han x C57/Bl cross ovulated a significantly increased number of hyperploid oocytes relative to parental strains or other hybrids. Djungarian hamsters ovulated diploid and hyperploid oocytes while NMRI/Han mice ovulated only diploid oocytes. Genetically-governed differences in response to the hormone were suggested to account for strain- and species-specific differences in aneuploidy outcome.

In effect, age-related changes in germ cell physiology and activities are forms of metabolic mediation of normal events. Observed effects of aging may reflect modification of a specific cellular process or an accumulation of changes that allow certain errors to occur more often than in physiologically younger individuals. In addition, the risk of a given chromosome being involved in nondisjunction and aneuploidy may change as the relative importance of each characteristic or activity changes with age (4). However, some specific causes for the relationship between increased aneuploidy incidence and advanced maternal age have been investigated. In their chiasma-hormonal hypothesis, Crowley et al. (22) proposed a relationship between the hormonally-governed rate of meiosis and chiasma terminalization. If changing

hormonal signals lengthen the meiotic cycle, chiasmata could be lost, generating univalents that might constitute a source of aneuploid gametes. This concept should be considered in the light of some question about chiasma terminalization as a true phenomenon (23, 24). At the structural level, Chandley and colleagues (20) have recently observed direct evidence for spindle abnormalities associated with aging in female CBA mice. Initial results have shown altered spindles accompanied by chromosome displacement from the metaphase plate in aged oocytes.

TARGETS AND MALSEGREGATION

Various chromosomal and extra-chromosomal structures and activities may be viewed as targets wherein aberrations leading to abnormal chromosome movement might arise. These structures and activities normally act in concert, they are designated separately here for convenience in discussing where the primary defects may occur or be expressed.

Spindle metabolism is a dynamic process dependent on close control of a complex intercellular environment, and it is not difficult to envision that microtubule malfunctions, whether or not they are related to aging, may often be at the heart of aneuploidy generation in germ cells. Recent biochemical and immunofluorescence studies have done much to elucidate the mechanics of chromosome movement during mitosis and have provided insight into a number of mechanisms by which aneuploid germ cells may arise.

As recently reviewed by Brinkley (25), McIntosh (26), and Nicklas (27), the primary structures involved in chromosome distribution include the centrosomes, kinetochores, and spindle microtubules (MTs). Accordingly, centrosomes allow the initiation of microtubule formation by lowering the activation energy for polymerization. The growth of spindle MTs involves rapid turnover of tubulin subunits and polarized elongation. Chromosomes are attached to spindle fibers at the kinetochore which serves as the interface between MTs and the centromere. The organization of the spindle, chromosomes, poles, and other elements at metaphase ensures that homologous chromosomes or sister chromatids move to opposite poles. Forces generated by a controlled disassembly of MTs that pulls chromosomes toward the poles, the interaction of actin and myosin, or a mechanical racheting by MT crossbridges have been proposed as possible sources of chromosome movement (28). From this brief

discussion, it is not difficult to postulate how changes in any part of this process could result in aneuploid cells. For example, if microtubule polymerization is inhibited (e.g., the centrosomes do not initiate polymerization, or the intracellular environment does not support polymerization), chromosome distribution could become random. If spindles do not attach the kinetochores, chromosomes may lag, potentially leading to malsegregation and aneuploidy.

One model for aneuploidy induction based upon chromosome-spindle interactions has been proposed by Ford et al. (29). The authors investigated the phenomenon of "chromosome displacement" in mitotic cell metaphases prepared without colchicine or hypotonic treatments. Chromosomes observed in the center of the hollow spindle rather than along the ring structure at its circumference were interpreted as displaced from the spindle apparatus. It was suggested that this displacement could lead to malsegregation and aneuploidy. In support of this hypothesis, individual autosomes from human lymphocytes were noted to be displaced with the same relative frequencies as they are known to be involved in aneuploidy. In addition, conditions promoting displacement, including unfavorable pH and increased calcium, increased the incidence of aneuploidy. Chromosome displacement provides a mechanism whereby hypoploid cells can arise without accompanying hyperploidy.

A number of regulatory molecules may affect aneuploidy generation via interactions with spindle metabolism. As an example, Margolis and Job (30) presented evidence that a microtubule-associated polypeptide alters the equilibrium of microtubules in vitro by blocking disassembly. The effect can be reversed by calmodulin or phosphorylation. Calmodulin may also serve to regulate the movement of microtubules attached to chromosomes (30).

Structural changes in chromosomes can be involved in aneuploidy in diverse ways. Translocations forming quadrivalents in meiosis may undergo segregational errors. Kinetochore-associated growth and organization of spindle fibers appear to be critical to the construction of the bipolar spindle and subsequent chromatid segregation (31). This implies that the chromosomes themselves are active in directing spindle assembly and that kinetochore disruption may undermine the general framework for normal chromosome movement.

Mutagen- and carcinogen-induced damage to kinetochores has been described (25). It seems reasonable that such damage, regardless of origin, could also affect centromere separation. This process, while normally ordered, may not always operate perfectly. Studies with several organisms have indicated that one of the homologues in a bivalent can occasionally undergo centromere division prematurely at the first meiotic division (6). Metaphase II cells with single chromatids have, in fact, been observed in mice (32, 33). Vig (34) has described the phenomenon of genetically controlled, nonrandom, sequential separation of mitotic centromeres for several organisms. Chromosomes which, for whatever reason, deviate from their scheduled time of separation, may not attach to spindle fibers (e.g., if separation preceded spindle formation) (35).

Unique DNA replication and recombination associated with meiotic homologue pairing and crossing over and attendant regulatory processes may represent critically important events in the generation of aneuploidy. A meiotic phenomenon potentially regulated by genetic control is the sequence of desynapsis of the synaptonemal complex (SC) during meiotic prophase. The formation of the SC is a physical manifestation of the synapsis of meiotic bivalents (36). Since synapsis and crossing over are important to normal disjunction

and segregation, direct observation of the structure and behavior of SCs provides novel insight into the role of homologous chromosome synapsis, crossing over, and desynapsis in the generation of aneuploid germ cells (37). Speed and Chandley (38) observed premature desynapsis of bivalent 19 in Swiss and CBA strain mouse oocytes and suggested that this event is a normal feature of mouse oocyte development. As these authors have suggested, homologue separation out of sequence in meiosis could result in malsegregation and aneuploidy.

The synaptonemal complex (SC) may be important to the generation of aneuploid germ cells in other ways. Stern and Hotta (39) have discussed the cellular events associated with synapsis in terms of both the initiation and subsequent functions of synapsis. Their work with Lilium demonstrated the critical function of a group of DNA sequences replicated during zygotene (ZygDNA) whose behavior coordinates with and possibly relates to chromosome pairing. Briefly, in Lilium, microsporocytes become irreversibly committed to meiosis at the time of suppression of ZygDNA replication by a regulating molecule, the L-protein. The ZygDNA acts as a structural component of synapsis and is transcribed at this time. ZygDNA sequences appear to be conserved across phylogeny (40) as important components of the meiotic process. Any inhibition of L-protein synthesis or function could interfere with the commitment to meiosis in general or with homologue pairing in particular. DNA synthesis also occurs during pachytene in both Lilium and mammals (41). This is a DNA repair process induced in response to nicking following the completion of chromosome pairing and is potentially involved in the initiation of meiotic recombination. Although the exact details of the roles played by specialized DNA sequences and regulatory molecules in effecting synapsis are not fully defined biochemically, one could easily speculate that aneuploidy

may have several sources of origin at the molecular level. Taken one step further, any interference with meiosis-specific proteins regulating crossing over could conceivably result in asynapsis or premature desynapsis, nondisjunction and, ultimately, aneuploidy.

Chromosome distribution without homologous pairing has been extensively studied in Drosophila (42). The possibility that this distributive pairing phenomenon, based on the interactions of chromosomes of approximately the same size, may also occur in humans has been suggested (43). Karyotype modifications, including heterozygous rearrangements or aneuploidy, could effect nonhomologous chromosome pairing, nonequational chromosome distribution, and aneuploid daughter cells (43).

Implications that reduced meiotic recombination may lead to aneuploidy stem from early genetic and cytological observations in aging rodents. In mouse backcross linkage experiments, Bodmer (44) found an age-dependent decrease in recombination frequency between 2 marker genes. The "production line" hypothesis mentioned earlier was founded on presumptive relationships between reduced chiasma frequencies, increased univalents, and increased aneuploidy observed in oocytes of older mice. Positioning of chiasmata at more terminal sites was also interpreted as a corollary to this process. Chiasmata normally hold homologues together until anaphase I. Reductions in crossovers and chiasmata should generate univalents which may segregate aimlessly-sometimes to the same pole and resulting daughter cell.

Some studies with rodent oocytes have confirmed various steps in the suggested recombination-to-aneuploidy sequence of events, while others have not. Reduced chiasma frequencies in older mice (34, 45) and hamsters (46) have been observed, and this is consistent with a more general concept of reduced recombination in older organisms (44). Yet, in another mouse breeding

study (47) and in cytological observations of translocation marker bivalents (48), age-related reductions in recombination could not be concluded. Characteristic increases of univalents in older animals have been reported in some (49) but not all (45) such studies. The correspondence of univalents with subsequent aneuploidy is another concern. Certain translocated mouse chromosomes have revealed similar elevations in univalents and secondary oocyte aneuploidy (48). However, in other studies of mouse meiotic complements, univalents were noted to occur with much greater frequency than secondary oocyte aneuploidy (32). Some enlightenment regarding this imbalance has come with studies of Chinese hamsters by Sugiwara and Mikamo (46). They showed that increased univalents and aneuploidy occurred in different chromosome groups. They further showed that in mice, univalents can be generated as artifacts with the slide preparation techniques commonly used in these studies (50). It would appear that many, if not all, of the observed univalents probably do not represent pathways to aneuploidy.

In our own studies with male Armenian hamsters, we have not detected any age effect upon meiotic recombination as evidenced by chiasma frequencies (51) and BrdUrd label patterns (unpublished observations). Hyperploidy appeared to be elevated in older animals. However, there was no indication that this occurred through the formation of univalents (51).

It remains to be determined conclusively whether there may be chromosome-specific low-level correlations between reduced chiasmata, some fraction of increased univalents, and aneuploidy. However, most current evidence does not support this premise. Speed and Chandley (38, 52) have suggested that fewer chiasmata and higher univalent frequencies may be due to the greater chromosome contraction characterizing older oocytes.

Throughout this section, various types of aberrations of chromosome structure and behavior which might translate to problems of distribution have been discussed. In its broadest sense, malsegregation can be interpreted to include any deviation from normal controlled movement of homologous chromosomes or sister chromatids to opposite poles and daughter cells. Whether these chromosomal entities become displaced from the spindle, fail to disjoin, or separate prematurely, the ensuing imperfect segregation can theoretically lead to aneuploidy.

SUMMARY

Unlike other forms of chromosomal abnormalities, the observation of a cell with one or a few extra or missing chromosomes typically reveals nothing about the source of the error. This has led to considerable speculation about the possible origins of aneuploidy. In natural situations where selective advantages are conferred, a single, regulated mechanism may be responsible for generating aneuploid germ cells. As a mistake, meiotic aneuploidy may be derived from a variety of possible mechanisms and be more sporadic and haphazard in its occurrence. Whether all or only a few of these mechanisms are actually operating as primary means can be argued to be of little consequence with regard to incidence or biological significance: different origins should theoretically give rise to similar outcomes.

Considering the plausible explanations, structural defects in particular seem likely to play an important role in aneuploidy production. In addition, the mechanical and biochemical complexity of meiosis suggests myriad specific events with theoretical potential to generate aneuploid germ cells. New information to modify existing theories and to generate alternatives is steadily becoming available. For example, vigorous testing of the long-standing "production line" hypothesis has resulted in the generation of some nonsupportive data and alternative explanations, making its validity more uncertain. Conflicting evidence that reduced meiotic recombination may be implicated is more understandable if failure to crossover is an occasional event secondary to a more central defect, e.g., aberrant synapsis/desynapsis. Biochemical and biophysical studies of the spindle and related apparatus are providing new insights as to basic physiological steps which may be vulnerable to aberrations. There are preliminary, very interesting observations in

experimental animals of age-related structural defects in spindles which, if they are also occurring in humans, could represent primary events predisposing to aneuploidy syndromes. If universally applicable mechanisms are responsible, they may be modified by individual differences in karyotype, metabolism, and aging.

The ideas surveyed here collectively portray the diffuseness of current concepts on the subject of meiotic aneuploidy and underscore the fundamental unresolved questions: How and to what extent do critical pre-aneuploidy changes occur in the chromosomes (structure, function), in their support matrix for movement, and/or in physiological regulatory influences upon chromosomal integrity, activity, or movement? Does meiotic chromosome differentiation from a mitotic state through morphological and metabolic transitions confer special vulnerabilities? Are meiotic pairing and recombination processes especially prone to errors which could lead to aneuploidy? Much emphasis is currently being given to the search for environmental agents which may predictably increase frequencies of meiotic aneuploidy and to the development of new assays for detecting these effects. Ultimately, these studies could help to answer many of the basic questions surrounding origins of meiotic aneuploidy, whether caused by genetic or degenerative events or by environmental induction.

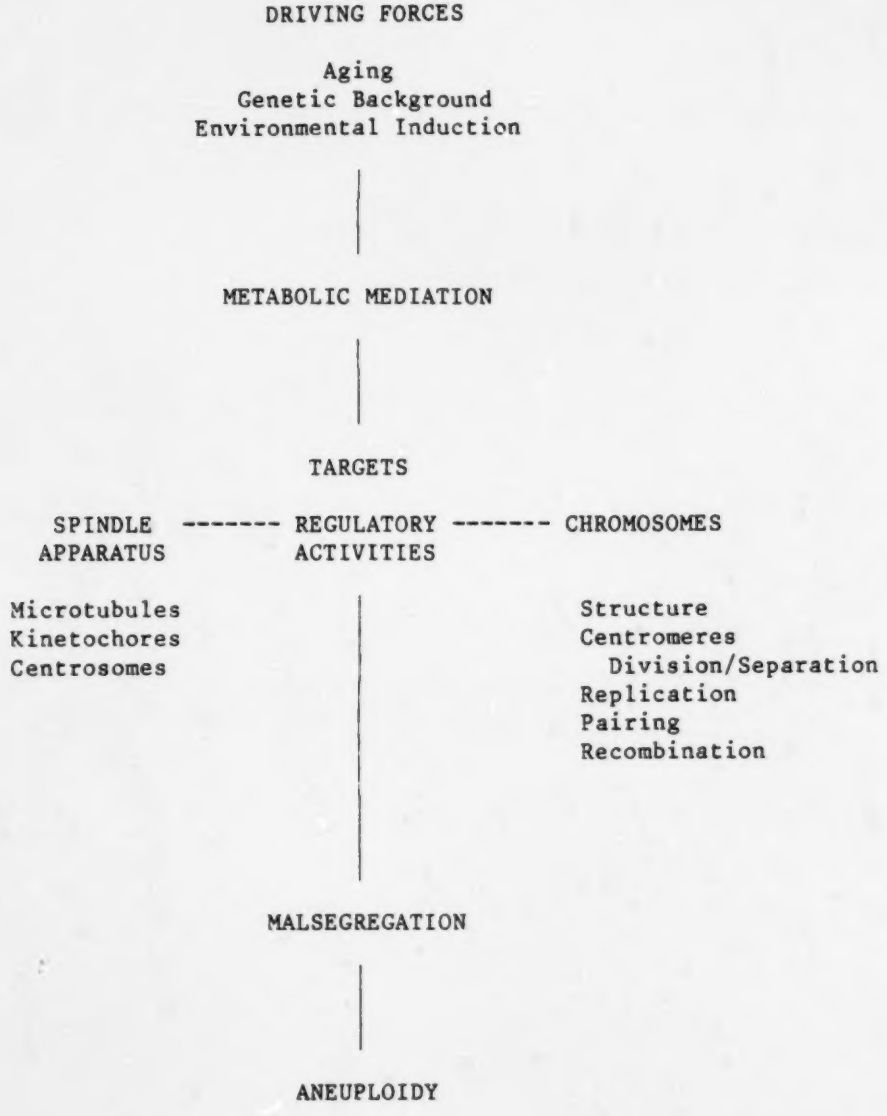

FIG. 1: An etiological overview of meiotic aneuploidy.

TABLE I. Meiotic cell stages and possible mechanisms implicated in aneuploidy

Germ cell lineage	Cell cycle stages	Possible mechanisms
Gonial cells	DNA synthesis	Misreplication
	Metaphase/anaphase	Chromosome malsegregation
Primary meiocytes	DNA synthesis	Misreplication
	Prophase	Synapsis anomalies Crossover failure Desynapsis anomalies
	Metaphase I/anaphase I	Homologue malsegregation
Secondary meiocytes	Metaphase II/anaphase II	Chromatid malsegregation

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